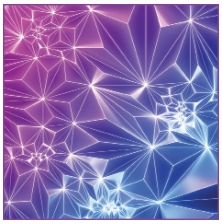

Fluorescence in the Sclera, Nails, and Teeth Secondary to Favipiravir Use for COVID-19 Infections

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Favipiravir, an antiviral agent originally used for influenza infections, has become popular due to its beneficial signals in coronavirus disease. It is currently used in some countries within COVID-19 treatment protocols. This is an initial report of favipiravir-related fluorescence observed in three healthcare providers working in the same ward in our hospital. All three individuals had been diagnosed with COVID-19 two months earlier and were treated with favipiravir. None of the three individuals received hydroxychloroquine or tetracyclines. Wood's light examination led to an incidental discovery of favipiravir-induced fluorescence involving the sclera, nails, and teeth. In all patients, white linear, square, and band-like specks of fluorescence were noticed on the sclera of both eyes, some teeth, and the proximal part of all fingernails and toenails. Exposure of the eyes to the Wood's light was for a brief duration of 3 to 5 seconds during examination and photodocumentation. Favipiravir might cause bright white fluorescence of nails, sclera, and teeth, detectable by Wood's light even two months after its cessation.
KEYWORDS: Favipiravir, nail, teeth, fluorescence, conjunctiva, COVID-19, coronavirus, Wood's light, UV lamp, polyvinylpyrrolidone.

The novel coronavirus pandemic has dawned a new era of medicine. Both novel COVID-19-related cutaneous signs and medication-induced cutaneous side effects are being increasingly encountered in clinical practice.

Currently, there is no specific antiviral therapy for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Favipiravir is a purine nucleoside analog and an antiviral agent that inhibits the RNA-dependent RNA polymerase of several RNA viruses.[1] It is utilized in some countries, including Turkey, for the treatment of COVID-19 infections. To date, no cutaneous adverse effect or manifestation liable to favipiravir has been reported.[2] This is an initial report of fluorescence secondary to treatment with favipiravir in three patients with COVID-19.

CASE REPORTS

Case 1. A 21-year-old female healthcare provider presented with a one-week history of white spots on her back. She had been diagnosed with COVID-19 infection two months prior. The diagnosis was presumptive and based on thorax CT scan revealing focal pulmonary ground glass appearance. SARS-CoV-2 rapid antigen, SARS-CoV-2 RT-PCR and Influenza antigen tests were all negative. She was hospitalized and treated with low-molecular weight (LMW) heparin plus favipiravir for five days. The recommended dosage of favipiravir was 3,200mg on Day 1, followed by 1200 mg/day on Days 2 to 5. Interestingly, SARS-CoV-2 total antibody and SARS-CoV-2 IgG and IgM tests performed 10 and 21 days after the infection yielded negative results.

Dermatological examination revealed there were hypopigmented macules with white scales on the back, typical of pityriasis versicolor. Wood's light examination in a dark room incidentally revealed chalk-white, band-like, square-shaped fluorescent marks involving the sclera of both eyes (Figures 1 and 2). Examination of oral mucosa and hair was normal. Crescent-shaped whitish fluorescence of fingernails and toenails was also observed.

Case 2. A 23-year-old female healthcare worker was under follow up for focal vitiligo in our department for the past two years. She had been definitively diagnosed with COVID-19 infection two months prior; both SARS-CoV-2 rapid antigen and SARS-CoV-2 RT-PCR tests were positive. She was hospitalized and treated with LMW heparin plus favipiravir for five days.

Dermatologic examination was normal except for three focal vitiligo macules measuring 1cm-size over the philtrum, right chest, and left wrist. There was remarkable chalk-white, crescent-shaped fluorescence of proximal fingernails and toenails under Wood's light (Figures 3 and 4). The appearance resembled French nail manicure. Prominent glowing white, irregular spots were also observed on the left upper incisor and canine teeth.

Case 3. A 26-year-old male healthcare worker without any

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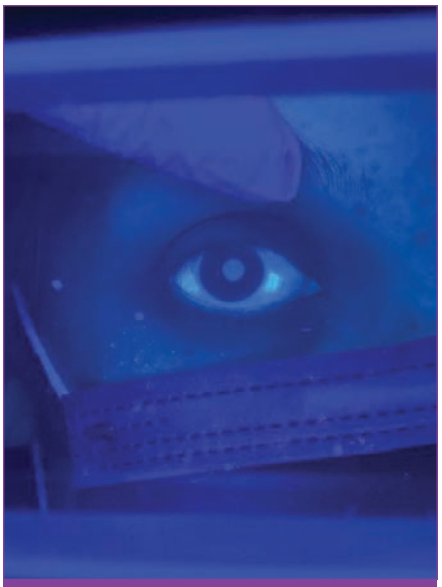

FIGURE 1. White-fluorescing square-shaped spots on the sclera of the right eye

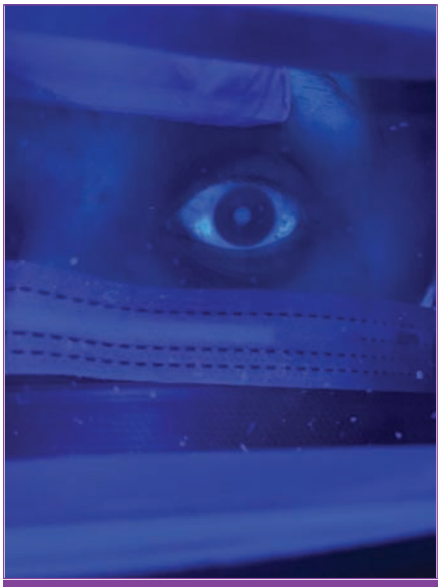

FIGURE 2. White-fluorescing irregular band-like spots on the sclera of the left eye

immediately apparent dermatological issues visited our department and requested to be examined under Wood's light. He had received a five-day course of favipiravir two months ago for a definitive diagnosis of COVID-19 infection.

Wood's light examination revealed chalk-white, crescent-shaped fluorescence of the proximal fingernails and toenails as well as tiny linear whitish specks of fluorescence involving the sclera of both eyes.

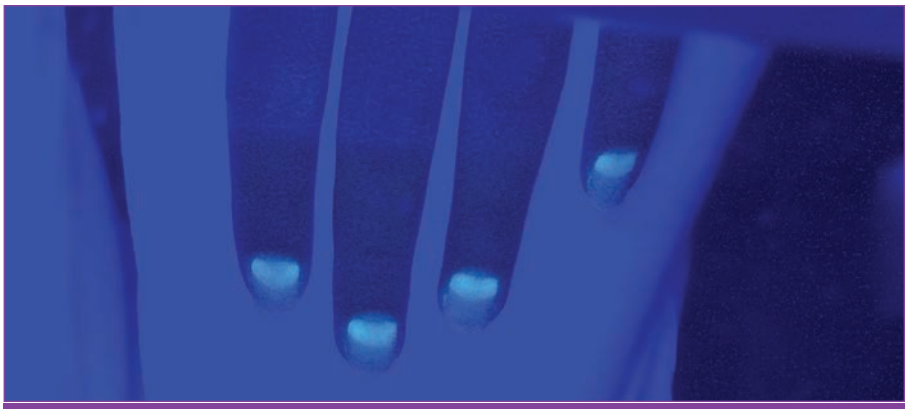

FIGURE 3. Chalk-white, crescent-shaped fluorescence of proximal fingernails parallel to lunula

FIGURE 4. Chalk-white, crescent-shaped fluorescence over lunula of toenails

DISCUSSION

Half-moon-shaped white fluorescence of fingernails appearing under ultraviolet (UV) lamp was originally observed in a textile factory in Denizli Organized Industrial Zone of Turkey.[3] Soon, it was evident that nail fluorescence existed only in patients who had received hydroxychloroquine or favipiravir for COVID-19 infection.

National guidelines in Turkey at the time of this observation recommend a five-day course of either favipiravir or hydroxychloroquine in uncomplicated ambulatory patients with COVID-19 infection.[4] All three patients presented herein had received favipiravir for five days at the recommended doses. Although white fluorescence of nails under Wood's light as a manifestation of coronavirus treatment has been discovered by the public and published in press media, at the time we observed these three patients, there had been no reports published in the medical literature. In addition to nail fluorescence, this paper contributes by adding whitish fluorescence of the sclera and teeth as manifestations of favipiravir use.

Some oral medications, such as tetracyclines and quinacrine, are acknowledged for their deposition in nails, teeth, and conjunctival tissues and emission of bright yellow fluorescence under Wood's light.[5-8] However, this phenomenon is dose-dependent and usually develops after a prolonged treatment period. It was fascinating to observe fluorescing deposits two months after only a five-day course of favipiravir. Greenish scleral deposits as a side effect of tetracycline congeners have been reported previously.[5] However, fluorescence of whole or part of sclera as a manifestation of oral medication intake has not been documented. In one of our patients, some of the teeth had demonstrated white specks of fluorescence as well. Staining of permanent adult dentition by tetracyclines has been attributed to extrinsic deposition of the medication or its metabolites on the

surface of teeth and discoloration upon chelation or oxidation.[6] A similar mechanism might be operative in favipiravir-induced teeth fluorescence.

Novel findings related either to the coronavirus itself or to medications used for its treatment continue to accumulate in the medical literature. So far, two cases regarding the nail manifestations of COVID-19 have been published. The "red half-moon nail sign" refers to red or violet half-moon-shaped discoloration surrounding the distal margin of lunula.[9,10] It has been reported as a manifestation of the coronavirus infection itself, and the pathogenesis has been ascribed to microvascular injury secondary to inflammation and vascular occlusion.[9] It is of note that one of the reported patients had history of antiviral use[9] and that both reports lacked the outcome of Wood's light examination. In our opinion, the possibility that "red half-moon nail sign" could be a manifestation of medication use, rather than being pathognomonic for COVID-19 infection, should also be explored.

Favipiravir 200mg tablets contain polyvinylpyrrolidones as excipients. Poly(N-vinylpyrrolidone) (PVP) is a substance with strong intrinsic fluorescent properties.[11] PVP is assumed to account for the bright white fluorescence observed in patients treated with favipiravir. Several new nanotechnology-based antiviral medications have been reported to contain PVP ring(s).[12]

CONCLUSION

It is likely that more patients will receive favipiravir or structurally similar antiviral medication for COVID-19 until the pandemic is adequately controlled. In our institution, a multidisciplinary clinicopathological follow up study is underway to assess the potential medical consequences of favipiravir fluorescence, and to determine whether the fluorescence is temporary or persistent.

REFERENCES

1. Boretti A. Favipiravir use for SARS CoV-2 infection. *Pharmacol Rep.* 2020;72:1542-1552.
2. Martinez-Lopez A, Cuenca-Barrales C, Montero-Vilchez T, et al. Review of adverse cutaneous reactions of pharmacologic interventions for COVID-19: A guide for the dermatologist. *J Am Acad Dermatol.* 2020;83:1738-1748.
3. Newsbeezer. The truth was spread as an "alternative to the corona test". Available at: https://newsbeezer.com/turkeyeng/the-truth-was-spread-as-an-alternative-to-the-corona-test/
4. COVID-19 Rehberi - T.C. Sağlık Bakanlığı. Available at: https://covid19.saglik.gov.tr/TR-66301/covid-19-rehberi.html
5. Morrison VL, Kikkawa DO, Herndier BG. Tetracycline induced green conjunctival pigment deposits. *Br J Ophthalmol.* 2005;89:1372-1373.
6. Ayaslioglu E, Erkek E, Oba AA, Cebecioğlu E. Doxycycline-induced staining of permanent adult dentition. *Aust Dent J*. 2005;50:273-275.
7. Gupta LK, Singhi MK. Wood's lamp. *Indian J Dermatol Venereol Leprol.* 2004;70:131-135.
8. Kierland RR, Sheard C, Mason HL, Lobitz WC. Fluorescence of nails from quinacrine hydrochloride. *J Am Med Assoc.* 1946;131:809.
9. Neri I, Guglielmo A, Virdi A, et al. The red half-moon nail sign: a novel manifestation of coronavirus infection. *J Eur Acad Dermatol Venereol.* 2020;34:e663-e665.
10. Méndez-Flores S, Zaladonis A, Valdes-Rodriguez R. COVID-19 and nail manifestation: be on the lookout for the red half-moon nail sign. *Int J Dermatol.* 2020;59:1414.
11. Song G, Lin Y, Zhu Z, et al. Strong fluorescence of poly(N-vinylpyrrolidone) and its oxidized hydrolyzate. *Macromol Rapid Commun.* 2015;36:278-285.
12. Sacco MD, Ma C, Lagarias P, et al. Structure and inhibition of the SARS-CoV-2 main protease reveal strategy for developing dual inhibitors against Mpro and cathepsin L. *Sci Adv.* 2020;6:eabe0751. JCAD